REMARKS/ARGUMENTS

Specification Amendments

By the present amendment, the specification, at page 1, line 2, has been amended to add a proper reference to all applications being relied on for claims for priority under Sections 371 and 119(e).

Claim Amendments

By the present amendment, claims 53 and 55 have been rewritten in independent form. Claim 55 has been further amended to add the proviso that, when the cells are peripheral neurons, the propargylamine is not R-deprenyl or R-desmethyldeprenyl. Claims 67 and 70 have been amended to add the proviso that the propargylamine is not R-deprenyl, R-desmethyldeprenyl or rasagaline. Claim 69 has been amended to correct a typographical error in its dependency. Claims 78 and 79 have been cancelled. Claims 81-106 are new. New claims 81, 83, 84, 87 and 89 correspond to the subject matter of claims 56, 58, 57 and 60 (both combined into 84), 66 and 64 respectfully, but depend on independent claim 53. New claims 82, 85, 86, 88 and 90 correspond to the subject matter of claims 56, 58, 57 and 60 (both combined into 86), 66 and 64 respectfully, but depend on independent claim 55. New claims 91-93 are dependent on claims 52, 53 and 55 respectfully, and further define the antineoplastic drug to be selected from the classes of drugs listed on page 10, lines 17-19, of the application as filed. New claims 94-96 are dependent on claims 52, 53 and 55 respectfully, and further define the antineoplastic drug to be selected from the group of drugs listed on page 10, lines 20-27, of the application as filed. New claims 97-99 are dependent on claims 52, 53 and 55 respectfully, and further define the antineoplastic drug to be selected from the group of drugs listed in claim 68. New claims 100-103 are dependent on claims 57, 60, 84 and 86 respectfully, and further define the

antineoplastic drug to be cisplatinum. New claim 104 is dependent on claim 67 and further defines the cancer to be one that involves cells mutant in p53. Support for this claim can be found on page 13, lines 28-31, and page 15, lines 27-28, of the application as filed. New claim 105 depends on claim 104 and further defines the cancer to be selected from certain cancers listed on page 9, line 32, to page 10, line 10, of the application as filed. New claim 106 is dependent on claim 55, and adds the proviso that the propargylamine is not rasagiline

The amendments have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicant reserves the right to file any of the deleted subject matter in a further continuation, continuation-in-part or divisional application. No new matter has been entered by the present amendment.

The Official Action dated April 10, 2003 has been carefully considered. It is believed that the amended claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 USC §112, First Paragraph

Enablement

Claims 52-80 have been rejected under 35 USC §112, First Paragraph, because the Examiner contends that the application, while being enabling for the use of 1) R-2HPA, R-2HMP or deprenyl in combination with 2) histindol or cisplatinum, respectively to increase activity and/or treat cancer, it does not reasonably provide enablement for the use of propargylamines in combination with "antineoplastic agents" generally. The Applicants respectfully disagree with the Examiner for the reasons that follow.

The Examiner sets out his objections under four headings, the response to each of which will be provided below in the order in which they appear in the Office Action.

1. The nature of the invention, state of the prior art, relative skill of those in th art and the predictability of the art

The Examiner contends that the art to which the instant invention relates involves a relatively high degree of unpredictability and refers to U.S. Patent 6,465,448 (hereinafter "Gerson") as a "standard publication in the art and as such is directed to those having ordinary skill in the art". The Examiner concludes that this publication demonstrates the unpredictability of the claimed subject matter in the present application. The statement in Gerson (column 1, lines 56-60) particularly referred to by the Examiner reads as follows: "These conditions require a great deal of empirical testing of agents known to have anticancer properties with agents that either may have anticancer properties, or that may augment the first agent in other ways."

The Examiner provides no justification for claiming that this patent is a standard publication. It is debatable that such a recent patent (issued in October of 2002) would be widely accepted already as a standard. Further the above statement found in Gerson is made without any supporting evidence or references cited in support. The Applicants submit that the comments found in Gerson are not true for all drugs and all combinations of drugs and for all cancers for the reason provided below.

It is reasonable to assume that finding a combination of drugs that meets the required criteria would be easier (i.e. requiring less experimentation) if at least one of the pair of drugs was part of a set, all the members of which function by means of a

common mechanism. The propargylamines of the present invention constitute such a set of drugs, the common mechanism involving p53 (see page 13, lines 28-31, and page 15, lines 27-28, of the application as filed). Here the common functional grouping is the propargylamine and the Applicants have shown that both aliphatic and aromatic (phenyl) derivatives of these compounds are active. The Applicants submit that the demonstration that these representative propargylamines have the claimed activities is sufficient to prove the concept and establish the conditions necessary for successful treatment using any of the claimed propargylamines. To a person skilled in the art, it is a reasonable assumption that if the active functional group remains constant (i.e. the propargymamine), moderate differences between molecules in terms of aliphatic chain length and non-chiral branching would not be predicted to dramatically alter treatment potency or efficacy.

With respect to the scope of the antineoplastic agent, and in support of the Applicants' contention that the instant invention does not involve a relatively high degree of unpredictability, is the fact that Warrington has demonstrated in several published papers (see the references cited in the application on page 15, line 29, to page 16, line 11, particularly the review in: Drugs of the Future (1993) 18:743-9, a copy of which has been provided in a Supplementary Information Disclosure Statement, submitted herewith) that L-histidinol, in combination with each of the six antineoplastic drugs recited in claim 68 of the present application (cytosine arabinoside, cis-platinum, cyclophosphamide, adriamycin, daunomycin and 5-fluorouracil), produces the same effects (rescuing/protecting normal cells, enhancing sensitivity of the tumor to killing, and overcoming drug resistance) as those claimed for the propargylamines of the present application, although L-histidinol possesses a dramatically lower potency (about one million times less potent). This suggests that L-histidinol and the propargylamines of the present application function by much the same mechanism. It is logical therefore

to deduce that if L-histidinol in combination with all six antineoplastic drugs (separately) elicits the claimed properties, then the claimed propargylamines in combination with all six antineoplastic drugs, at least, should also elicit the claimed properties.

The six antineoplastic drugs tested by Warrington represent a variety of chemical (alkylating agents, antitumor antibiotics and antimetabolites) and functional (Class I, cycle non-specific; Class II, acts in S phase; Class III, cycle specific) classes. Warrington has also shown that antineoplastic drugs which are mitotic inhibitors (vinblastine) in combination with L-histidinol possess the same properties as those antineoplastic drugs claimed in the present application (Warrington, R.C. Biochemistrty & Cell Biology (1992) 70:365-375, cited in application and copy provided in Supplementary IDS submitted herewith). Thus, even though many of these agents have markedly different modes of action and proliferation and/or phase dependencies for cell-killing, L-histidinol has essentially a uniform influence on their cytotoxicities. As stated in Warrington and Fang, J. Nat. Cancer Inst. (1985) 71, page 1076 (cited in application and copy provided in Supplementary IDS, submitted herewith): "Assays with a wide variety of antineoplastic agents revealed that histidinol generally increased the vulnerability of the cell lines to the agents in a remarkably similar and dose-dependent manner".

In summary, and as described on page 14, lines 6-11, of the application as filed, since histidinol modulates a variety of chemotherapies and the compounds of the present invention have the same action as histidinol, the compounds of the present invention should, at least, also modulate the same chemotherapies, one example of which is specifically described as a working example.

For clarification, the Applicants would like to point out that the Examiner appears to have misunderstood the function of L-histidinol. Histidinol is NOT an antineoplastic drug used in combination with the propargylamines (as the Examiner seems to suggest), but is, like the propargylamines, an antineoplastic modulator (see page 15, lines 15-18, of the present application). In the present application, it served as a comparative, although much less potent, control. The use of L-histidinol is not claimed in the present application.

On the basis of the above arguments, the Applicant submits that the Examiner's statement that the present invention "involves a relatively high degree of unpredictability" is not valid and therefore undue additional experimentation would not be necessary to make use of the entire scope of the invention as claimed in the present application by a person skilled in the art.

2. The Breadth of the Claims

It was noted by the Examiner that all the claims are broad and inclusive of many combinations of propargylamines and antineoplastic agents, with no claim specifically reciting a combination of one of the propargylamines with cisplatinum. Arguments presented above in support of the breadth of the claims with respect to the identity of the propargylamine and the antineoplastic agent, apply here as well. The Applicant wishes to point out that they have added, new claims 91-103 directed to methods wherein the antineoplastic drug is selected from a variety of those listed on page 10, lines 17-27 of the application as filed.

The Examiner further states that no specific cancer types are claimed, and comments that success in treating one type of cancer does not guarantee success in treating other unrelated types of cancer. The question is: what constitutes unrelated

types of cancer? The mechanisms of many types of cancer are sufficiently the same that it would not be necessary to test a drug combination for every conceivable form of cancer, accordingly, the Applicants submit that a skilled artisan would be able to predict success in treating other forms of cancer from success in treating one. In support of this is the work of Warrington (cited hereinabove) where he demonstrated that L-histidinol is a modulator in many different normal and tumor cell lines of both animal and human origin, as well as in *in vivo* tumors representing models of different types of cancers including leukemia, melanoma and colorectal carcinomas. Warrington has demonstrated that for most cell lines, the results of histidinol-antineoplastic treatment are predictive of what occurs *in vivo*. He also showed that the results from human tumor cell studies with histidinol and antitumor drugs are qualitatively and quantitatively similar to those of their mouse counterparts. Using the same arguments presented above we submit that the propargylamines would be successful in these models as well, without undue experimentation.

A particular example of a broad class of cancers that can be expected to be successfully treated using the method of the invention are those cancers involving a common underlying mechanism. Thus, cancers involving a mutation in p53, a double deletion, or significant changes in the activity of p53 are candidates reasonably predicted to be amenable to treatment by propargylamines in combination with antineoplastic drugs (see page 13, lines 28-31, and page 15, lines 27-28, of the application as filed). Furthermore, extensive clinical data suggest that the presence of p53 mutated or deleted forms of disease have generally a poor prognosis because of the chemoresistant (and radioresistant) phenotype resulting from the alteration of the p53 status. New dependent claim 104 has been added that is specifies that the method of treating cancers involves cells that are mutant in p53 and new dependent claim 105 lists several specific cancers of this type.

Further in regard to the breadth of scope around the types of cancers, the Applicants note that the Gerson patent, which the Examiner considers to be a standard publication in the art, includes a claims (in particular claims 1-8) to methods of treat cancer in general with no limitation on the type of cancer that may be treated. Further claim 15 specifies 11 types of apparently quite different cancers, without any evidence showing that testing was done on models of any of them, or that they involve a common underlying property which would render all of them amenable to the treatment claimed therein. All testing was done on one or both of two cell lines (HCT116 and SW480); of the eight working examples provided in the specification only two (#4 and #8) provided a link to a specific type of cancer, namely colon cancer. Because the Gerson patent has issued it seems reasonable to assume that such broad claims are indeed patentable even without experiment support that the treatment is successful in each and every one of the claimed cancers.

In light of the above arguments, the Applicant submits that the breath of the claims as filed is supported by the information in the application as filed in combination with the knowledge of a person skilled in the art and accordingly no amendment of claims 52-80, is necessary.

3. The amount of direction or guidance provided and the presence or absence of working examples

In this subsection the Examiner expresses concern that the only guidance for using propargylamines to increase the activity of antineoplastic agents or to treat cancer is that described for the specific combinations actually tested in the working examples (R-2HPA, R-2HMP and deprenyl in combination with cisplatin). The Applicants' arguments presented hereinabove that the compounds of the present

invention are active by the same mechanism as L-histidinol in modulating antineoplastic drugs again leads to the conclusion that the present invention does NOT involve a high degree of unpredictability, and therefore the descriptions in the working examples provided are transferrable to drug combinations other than those actually described in the Examples.

4. The quantity of experimentation necessary

Again, arguments in subsections 1 and 2, hereinabove, demonstrate that undue experimentation would NOT be necessary to extend the described method to combinations of other propargylamines with other antineoplastics and for other cancers. For this reason the Application submits that the Examiner's statement that "Testing would have to be conducted on each particular propargylamine and antineoplastic agent, across a variety of representative cancer types, with no expectation of success being present prior to testing" is not correct.

The inventors do not deny that some additional experimentation might be necessary by a person wishing to make use of the invention to optimize potency/efficacy for propargylamines and antineoplastic drugs other than those described in the working examples, but in light of the arguments presented above the inventors maintain that such additional experimentation would not be excessive, certainly not beyond what is customarily accepted.

In light of the above arguments, the Applicants respectfully request that the Examiner's objections to claim 52-80 under 35 USC §112, First Paragraph, be withdrawn.

35 USC §102(e): Anticipation

The Examiner has rejected claims 52-56, 62, 64, 66-71, 77 and 78 under 35 USC §102(e) as being anticipated by Bobotas (US Patent No. 6,239,181). The Examiner states that the Bobotas patent on the use of selegiline (R-deprenyl) to protect normal peripheral nerve cells from the cytotoxic effects of neoplastic agents anticipates the above-listed claims in the present application. The Applicants submit that this is true only in part.

The Applicants submit that the use of deprenyl to protect normal peripheral nerve cells from the cytotoxic effects of antineoplastic drugs as described in Bobotas anticipates only a portion of claims 55, 67-71, 77 and 78 and have amended these claims to remove the anticipated subject matter.

The Applicants submit that the use of propargylamines (including deprenyl) as antineoplastic modulators to enhance the activity of antineoplastic drugs and to overcome drug resistance in tumors is not described by Bobotas and therefore Bobotas does not anticipate claims 52-54, 56, 62, 64 and 66 of the present application. Specifically, independent claim 52 refers to enhancing the activity of an antineoplastic drug in combination with a propargylamine. It does not refer to providing protection for normal cells, therefore, the Applicant submits that claim 52, and claims dependent thereon, require no amendments in claim scope. Likewise, claim 53, which has been re-written in independent form in the present amendment, is directed to a method of increasing the sensitivity of a tumor to an antinoplastic drug which is an activity that is not described in Bobotas and therefore this claim, and claims dependent thereon, require no amendments in claim scope.

Regarding claim 53, and claim 54 dependent thereon, the Examiner seems to contend that because the prior art daily non-oral dosages of selegiline (deprenyl) are similar to those for many aromatic propargylamines claimed in the present application (which may be up to ten fold higher than dosages for the aliphatic propargylamines) "increased drug sensitivity (and by implication reduced drug resistance) would be an inherent feature of the prior art methods." The Applicants respectfully disagree with this statement. The so-called inherent features (i.e. increased drug sensitivity and reduced drug resistance) of deprenyl, were not explicitly or implicitly described in Bobotas and therefore should not be considered to anticipate the same in the present application. Furthermore, these properties (enhanced killing of cancer cells and overcoming drug resistance) are not necessarily inherent to all compounds which protect normal cells from the cytotoxic effects of neoplastic agents. There are many compounds which are able to protect normal cells, but because of the much different physiology of cancer cells, there are very few compounds like those of the present invention which are able to enhance the killing and overcome the resistance of cancer cells to antineoplastic drugs (as well as protect normal cells).

Claim 55, which has been amended to be written in independent form is directed to a method for protecting normal cells from the cytotoxic effects of an antineoplastic drug comprising administering an effective amount of a propargylamine of Formula I. The Applicant submits that protection of normal non-neuronal cells and any normal cells of the CNS should still be available even in light of Bobotas. It is relevant to note here that it has been demonstrated that chemotherapy-induced alopecia (hair loss) is the single biggest reason patients refuse therapy. Therefore, protecting hair cells (i.e. non-neuronal peripheral normal cells) would be enormously beneficial. Chemotherapies kill these cells by a p53-dependant apoptotic process, which is treatable with the method of the present invention. Protection of these peripheral non-

neuronal normal cells is not covered by the Bobotas patent. Of course, even more important than the psychological factor of hair loss in determining acceptance of therapy by patients is the life-and-death fact that the major dose-limiting consideration is the damage to and death of normal bone marrow stem cells (peripheral, non-neuronal), which we have shown are protected from the toxic effects of antineoplastic drugs by the propargylamines, both *in vitro* and *in vivo*.

In light of the above amendments and arguments, the Applicants request that the Examiner's rejection of claims 52-56, 62, 64, 66-71, 77 and 78 under 35 USC §102(e), be withdrawn.

35 USC §103: Obviousness

Claims 59, 63, 74 and 79 have been rejected under 35 USC §103 as being obvious in light of Bobotas (US Patent No. 6,239,181). The Examiner contends that the disclosure in Bobotas of the use of deprenyl in protecting peripheral nerves from the cytotoxic effects of antineoplastic agents, renders the use of its homolog, desmethyldeprenyl obvious.

The Applicants wish to point out that claims 59 and 63 both depend on claim 52, which, as argued above, they submit is not anticipated by Bobotas. The Applicants further submit that Bobotas does not explicitly or implicitly teach the that deprenyl, or homologs thereof, including desmethyldeprenyl, has the activity of increasing drug activity (as claimed in claim 52) and therefore this property in deprenyl, or homologs thereof, is not obvious from the Bobotas document. There are many compounds which are able to protect normal cells, but because of the much different physiology of cancer cells, there are very few compounds like those of the present invention which are able to enhance the killing and overcome the resistance of cancer

cells to antineoplastic drugs (as well as protect normal cells). Claim 74 depends on Claim 70 which has been amended to exclude both R-deprenyl and R-desmethyldeprenyl, which should overcome this rejection. Claim 79 has been cancelled in the present amendment.

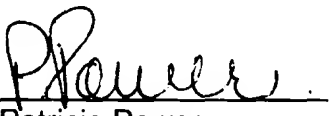
In light of the above amendments and arguments, the Applicants request that the Examiner's rejection of claims 59, 63, 74 and 79 under 35 USC §103, be withdrawn.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the

application in greater detail, he is kindly requested to contact the undersigned by telephone at (416) 364-7311 at his convenience.

Respectfully submitted,

Bereskin & Parr

By 

Patricia Power
Reg. No. 51,379
Tel: 416-957-1683